Noninvasive characterization of lymphatic flow velocity using principles of spin labeling

Swati Rane[1], Paula Donahue[2], John Jordi[3], John C Gore[1,4], and Manus Donahue[1]

[1]Radiology and Radiological Sciences, Vanderbilt University Institute of Imaging Science, Vanderbilt University, Nashville, TN, United States, [2]Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN, United States, [3]Lymphedema Clinic, Siskin Hospital, Chattanooga, TN, United States, [4]Biomedical Engineering, Vanderbilt University, Nashville, TN, United States

INTRODUCTION: The overall aim of this study is to exploit principles of spin labeling to magnetically tag water spins in human lymphatic fluid and for the first time noninvasively characterize the flow of lymphatic fluid to axillary lymph nodes. More specifically, breast cancer treatment related lymphedema (BCRL) is characterized by chronic and incurable swelling of the arm following axillary lymph node dissection and represents a major health and quality of life concern in developed nations. Of approximately 2.3 million breast cancer survivors in the United States, a significant proportion (19-33%) of patients undergoing axillary lymph node dissection and radiation therapy, develop BCRL with no routine imaging approaches available for identifying risk [1]. Lymphatic vessel contractility is hypothesized to correlate with BCRL risk, but clinical implementation of CT, optical, and MR lymphangiography techniques are complicated by requirements for ionizing radiation, specialized optical probes and fluorophores, and/or exogenous contrast agents, which collectively make these approaches only available in specialized centers. Noninvasive MRI techniques for assessing lymphatic flow and corresponding BCRL risk remain under-developed. Importantly, even basic measurements of 3.0T human lymphatic water relaxation times (T_1 and T_2) have not been performed. However, the principles of lymphatic flow are analogous to those of blood flow, which has been successfully measured with MRI for many years. For instance, the lymphatic system is unidirectional and open-ended, in which lymphatic fluid is carried to nodes via lymphatic vessels through forces supplied by smooth muscle contractions. Thus, noninvasive arterial spin labeling (ASL) approaches, commonly employed to magnetically label blood water and quantify perfusion, could translate to lymphatic imaging [2]. This would greatly expand the imaging options for lymphedema, allowing for lymphatic flow velocity and volume to be quantified noninvasively *in vivo* using existing MRI equipment available in most hospitals. The major obstacles for extending principles of ASL to lymphatic spin labeling include (i) the slow velocity of lymphatic fluid relative to blood and (ii) increased field heterogeneity and radiofrequency (RF) labeling inefficiency in extremity regions. We hypothesize that these difficulties can be overcome by (i) lymphatic T_1 being much longer than blood water T_1, and (ii) applying multi-channel receive coils in conjunction with parallel RF-transmit technology. We report (i) T_1 and T_2 measurements of human lymphatic fluid at 3T, thereby providing a quantitative reference for lymphatic contrast characterization using MRI and (ii) feasibility of the lymphatic spin labeling approach, thereby providing a foundation for improved screening procedures of BCRL patients with the aim of guiding treatment in at-risk populations and preventing, or reducing, lymphedema-related morbidity.

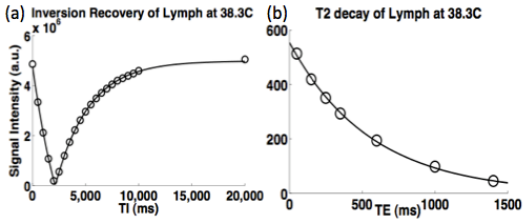

Fig. 1. *(a) Inversion recovery of lymph (line = three parameter fit, circles = data. (b) T2 decay (line = exponential fit, circles = data)*

METHODS: All volunteers provided consent in accordance with the local IRB. *Relaxation measurements:* Lymphatic fluid T_1 and T_2 were measured at 3T (Philips®) from human lymphatic fluid obtained from a subject (16yr/F) with a deep abdominal lymphatic shunt designed for manual drainage at the surface of the skin. A 200 mL sample was transported to the imaging facility immediately after extraction in a temperature-controlled box. The fluid was maintained at body temperature in the scanner using a water bath and monitored with a thermochromic thermometer. For T_1 measurement, an inversion recovery protocol was implemented with TR/TE=40000/28 ms and TI range=500–10000 ms (500 ms intervals), and with long TI=20000 ms. For T_2 measurement, a multi-echo, spin echo protocol was implemented with TR=2500 ms and TE=50, 150, 250, 350, 600, 1000, and 1400 ms. Measurements were repeated for three different samples, each obtained on different days. *In vivo experiments:* Labeling efficiency, fat suppression and signal-to-noise ratio (SNR) were optimized in preliminary methodology experiments. Subsequently, lymphatic spin labeling was assessed in healthy (n=6) volunteers at 3T using body two channel parallel transmit body coil in conjunction with a 16-channel torso receive coil and the following protocol: Diffusion weighted imaging with body signal suppression (DWIBS) to locate axillary nodes (TR/TE/TI= 8037/50/260 and b = 800s/mm^2; spatial resolution = 3x3x5 mm^3). An adiabatic pulsed (FAIR, [3]) spin labeling scan, parallel RF transmit, spatial resolution=3x3x5 mm^3, SPIR fat suppression (190 Hz), inversion time (TI) = 500–7500 ms (500 ms intervals), and single-shot gradient echo EPI readout to characterize lymphatic flow.

RESULTS AND DISCUSSION: ***Fig. 1*** shows the inversion recovery curve used for T_1 quantification (a) and the exponential decay used for T_2 quantification (b) from a representative fluid sample. Mean T_1 and T_2 values are tabulated in ***Table 1***; note that lymphatic T_1=3117 ms is approximately twice as long as blood water T_1, thereby suggesting that spin labeling experiments with a long post-labeling delay should be possible in lymphatic fluid. A DWIBS image (***Fig. 1a***) was used to identify the location of the lymph nodes on the spin labeling EPI image (***Fig 1b***). Kinetic curves in lymph nodes and arterial blood (***Fig. 1c***) demonstrate a typical blood kinetic curve, with delayed arrival of lymphatic fluid for labeling delay = 3500-5000 ms (example volunteer data shown). Note that it is not possible for the signal in the lymph node to arise from perfusion, as the blood T_1~1.5s would provide insufficient label at such a long post-labeling delay. Additionally note that lymphatic water $\Delta M/M_0$ in the axillary node is approximately a factor of 10 less than the blood water $\Delta M/M_0$ in the large vessel. However, $\Delta M/M_0$=0.04 is still 3-4 times higher than ASL-measured perfusion $\Delta M/M_0$ in cortex, thereby suggesting that this approach may have even greater sensitivity than perfusion imaging. The (mean ± std) transit time for lymph was 5083±970 ms and the time-to-peak (TTP) was 5833±876 ms (***Table 1***). Given a gap of 0.5 mm between the node and the adiabatic labeling pulse, this leads to an estimated lymphatic flow velocity of 5.9 cm/min, which is in approximate agreement with contrast-based approaches (8.9 cm/min hand-to-axillary mean velocity, [4]). Lymphatic quantification models, labeling efficiency improvements and patient applications are still required and comprise ongoing investigations in our lab. However, this study shows for the first time, the feasibility of using spin labeling principles to measure lymphatic flow to the axillary lymph nodes, an application which could have great benefit for stratifying lymphedema risk and guiding therapy decisions in patients following axillary lymph node dissection.

REFERENCES: 1. Langer I, et al. *Ann Surg*. 2007;245. [2] Detre J, et al. *MRM* 1992;23. [3] Kim S, et al. *MRM*. 1995;34. [4] Modi S, et al. *J Physiol.* 2007;15.

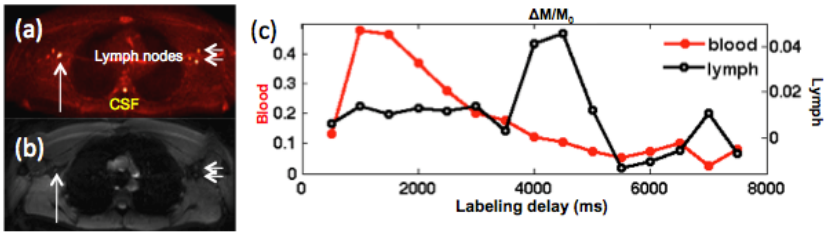

Fig. 2*. (a) DWIBS scan for node localization. (b) Control image from spin labeling scan showing axillary lymph node locations (arrows), (c) Kinetic curves for a blood vessel (red) and axillary lymph node (black). Lymphatic fluid arrival occurs at delay 3500-4000 ms in this subject.*

Lymph	Mean ± Std. Dev
T_1 (ms)	3117 ± 158
T_2 (ms)	605 ± 12
Transit time (ms)	5083 ± 970
TTP (ms)	5833 ± 876
Velocity (cm/min)	5.9

Table 1*. Lymph parameters.*